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October 15, 1992

Document Processing Center (TS-790)
Office of Pollution Prevention and Toxics
Environmental Protection Agency
401 M Street., S.W.
Washington, D.C. 20460
Attn: Section 8(e) Coordinator (CAP Agreement)

Dear Coordinator:

8ECAP-0025

On behalf of the Regulatee and pursuant to Unit II B.1.b. and Unit II C of the 6/28/91CAP Agreement, E.I. Du Pont de Nemours and Co. hereby submits (*in triplicate*) the attached studies. Submission of this information is voluntary and is occasioned by unilateral changes in EPA's standard as to what EPA now considers as reportable information. Regulatee's submission of information is made solely in response to the new EPA §8(e) reporting standards and is not an admission: (1) of TSCA violation or liability; (2) that Regulatee's activities with the study compounds reasonably support a conclusion of substantial health or environmental risk or (3) that the studies themselves reasonably support a conclusion of substantial health or environmental risk.

The "Reporting Guide" creates new TSCA 8(e) reporting criteria which were not previously announced by EPA in its 1978 Statement of Interpretation and Enforcement Policy, 43 Fed Reg 11110 (March 16, 1978). The "Reporting Guide states criteria which expands upon and conflicts with the 1978 Statement of Interpretation. Absent amendment of the Statement of Interpretation, the informal issuance of the "Reporting Guide" raises significant due processes issues and clouds the appropriate reporting standard by which regulated persons can assure TSCA Section 8(e) compliance.

For Regulatee,

Mark H. Christman
Counsel
Legal D-7158
1007 Market Street
Wilmington, DE 19898
(302) 774-6443

3/6/95

ATTACHMENT 1

Submission of information is made under the 6/28/91 CAP Agreement, Unit II. This submission is made voluntarily and is occasioned by recent changes in EPA's TSCA §8(e) reporting standard; such changes made, for the first time in 1991 and 1992 without prior notice and in violation of Regulatee's constitutional due process rights. Regulatee's submission of information under this changed standard is not a waiver of its due process rights; an admission of TSCA violation or liability, or an admission that Regulatee's activities with the study compounds reasonably support a conclusion of substantial risk to health or to the environment. Regulatee has historically relied in good faith upon the 1978 Statement of Interpretation and Enforcement Policy criteria for determining whether study information is reportable under TSCA §8(e), 43 Fed Reg 11110 (March 16, 1978). EPA has not, to date, amended this Statement of Interpretation.

After CAP registration, EPA provided the Regulatee the June 1, 1991 "TSCA Section 8(e) Reporting Guide". This "Guide" has been further amended by EPA, EPA letter, April 10, 1992. EPA has not indicated that the "Reporting Guide" or the April 1992 amendment supersedes the 1978 Statement of Interpretation. The "Reporting Guide" and April 1992 amendment substantively lowers the Statement of Interpretation 's TSCA §8(e) reporting standard[2]. This is particularly troublesome as the "Reporting Guide" states criteria, applied retroactively, which expands upon and conflicts with the Statement of Interpretation.[3] Absent amendment of the Statement of Interpretation, the informal issuance of the "Reporting Guide" and the April 1992 amendment clouds the appropriate standard by which regulated persons must assess information for purposes of TSCA §8(e).

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[2]In sharp contrast to the Agency's 1977 and 1978 actions to soliciting public comment on the proposed and final §8(e) Policy, EPA has unilaterally pronounced §8(e) substantive reporting criteria in the 1991 Section 8(e) Guide without public notice and comment, See 42 Fed Reg 45362 (9/9/77), "Notification of Substantial Risk under Section 8(e): Proposed Guidance".

[3]A comparison of the 1978 Statement of Interpretation and the 1992 "Reporting Guide" is a appended.

Throughout the CAP, EPA has mischaracterized the 1991 guidance as reflecting "longstanding" EPA policy concerning the standards by which toxicity information should be reviewed for purposes of §8(e) compliance. Regulatee recognizes that experience with the 1978 Statement of Interpretation may cause a review of its criteri. Regulatee supports and has no objection to the Agency's amending reporting criteria *provided that* such amendment is not applied to the regulated community in an unfair way. However, with the unilateral announcement of the CAP under the auspices of an OCM enforcement proceeding, EPA has wrought a terrific unfairness since much of the criteria EPA has espoused in the June 1991 Reporting Guide and in the Agency's April 2, 1992 amendment is new criteria which does not.exist in the 1978 Statement of Interpretation and Enforcement Policy.

The following examples of new criteria contained in the "Reporting Guide" that is not contained in the Statement of Interpretation follow:

o even though EPA expressly disclaims each "status report" as being preliminary evaluations that should not be regarded as final EPA policy or intent[4], the "Reporting Guide" gives the "status reports" great weight as "sound and adequate basis" from which to determine mandatory reporting obligations. ("Guide" at page 20).

o the "Reporting Guide" contains a matrix that establishes new numerical reporting "cutoff" concentrations for acute lethality information ("Guide" at p. 31). Neither this matrix nor the cutoff values therein are contained in the Statement of Interpretation. The regulated community was not made aware of these cutoff values prior to issuance of the "Reporting Guide" in June, 1991.

othe "Reporting Guide" states new specific definitional criteria with which the Agency, for the first time, defines as 'distinguishable neurotoxicological effects'; such criteria/guidance not expressed in the 1978 Statement of Interpretation.[5];

othe "Reporting Guide" provides new review/ reporting criteria for irritation and sensitization studies; such criteria not previously found in the 1978 Statement of Interpretation/Enforcement Policy.

othe "Reporting Guide" publicizes certain EPA Q/A criteria issued to the Monsanto Co. in 1989 which are not in the Statement of Interpretation; have never been published in the Federal Register or distributed by the EPA to the Regulatee. Such Q/A establishes new reporting criteria not previously found in the 1978 Statement of Interpretation/Enforcement Policy .

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[4]The 'status reports' address the significance, if any, of particular information reported to the Agency, rather than stating EPA's interpretation of §8(e) reporting criteria. In the infrequent instances in which the status reports contain discussion of reportability, the analysis is invariably quite limited, without substantial supporting scientific or legal rationale.

[5] *See, e.g,* 10/2/91 letter from Du Pont to EPA regarding the definition of 'serious and prolonged effects' as this term may relate to transient anesthetic effects observed at lethal levels; 10/1/91 letter from the American Petroleum Institute to EPA regarding clarification of the Reporting Guide criteria.

In discharging its responsibilities, an administrative agency must give the regulated community fair and adequate warning to as what constitutes noncompliance for which penalties may be assessed.

> Among the myriad applications of the due process clause is the fundamental principle that statutes and regulations which purport to govern conduct must give an adequate warning of what they command or forbid.... Even a regulation which governs purely economic or commercial activities, if its violation can engender penalties, must be so framed as to provide a constitutionally adequate warning to those whose activities are governed.

Diebold, Inc. v. Marshall, 585 F.2d 1327, 1335-36 (D.C. Cir. 1978). *See also*, Rollins Environemntal Services (NJ) Inc. v. U.S. Environmental Protection Agency, 937 F. 2d 649 (D.C. Cir. 1991).

While neither the are rules, This principle has been applied to hold that agency 'clarification', such as the Statement of Interpretation, the "Reporting Guide" nor the April 1992 amendments will not applied retroactively.

> ...a federal court will not retroactively apply an unforeseeable interpretation of an administrative regulation to the detriment of a regulated party on the theory that the post hoc interpretation asserted by the Agency is generally consistent with the policies underlying the Agency's regulatory program, when the semantic meaning of the regulations, as previously drafted and construed by the appropriate agency, does not support the interpretation which that agency urges upon the court.

Standard Oil Co. v. Federal Energy Administration, 453 F. Supp. 203, 240 (N.D. Ohio 1978), aff'd sub nom. Standard Oil Co. v. Department of Energy, 596 F.2d 1029 (Em. App. 1978):

The 1978 Statement of Interpretation does not provide adequate notice of, and indeed conflicts with, the Agency's current position at §8(e) requires reporting of all 'positive' toxicological findings without regard to an assessment of their relevance to human health. In accordance with the statute, EPA's 1978 Statement of Interpretation requires the regulated community to use scientific judgment to evaluate the significance of toxicological findings and to determining whether they reasonably support a conclusion of a substantial risk. Part V of the Statement of Interpretation urges persons to consider "the fact or probability" of an effect's occurrence. Similarly, the 1978 Statement of Interpretation stresses that an animal study is reportable only when "it contains reliable evidence ascribing the effect to the chemical." 43 Fed Reg. at 11112. Moreover, EPA's Statement of Interpretation defines the substantiality of risk as a function of both the seriousness of the effect and the probability of its occurrence. 43 Fed Reg 11110 (1978). Earlier Agency interpretation also emphasized the "substantial" nature of a §8(e) determination. See 42 Fed Reg 45362, 45363

(1977). [Section 8(e) findings require "extraordinary exposure to a chemical substance...which critically imperil human health or the environment"].

The recently issued "Reporting Guide" and April 1992 Amendment guidance requires reporting beyond and inconsistent with that required by the Statement of Interpretation. Given the statute and the Statement of Interpretation's explicit focus on substantial human or environmental risk, whether a substance poses a "substantial risk" of injury requires the application of scientific judgment to the available data on a case-by-case basis.

If an overall weight-of-evidence analysis indicates that this classification is unwarranted, reporting should be unnecessary under §8(e) because the available data will not "reasonably support the conclusion" that the chemical presents a substantial risk of serious adverse consequences to human health.

Neither the legislative history of §8(e) nor the plain meaning of the statute support EPA's recent lowering of the reporting threshold that TSCA §8(e) was intended to be a sweeping information gathering mechanism. In introducing the new version of the toxic substances legislation, Representative Eckhart included for the record discussion of the specific changes from the version of H. R. 10318 reported by the Consumer Protection and Finance Subcommittee in December 1975. One of these changes was to modify the standard for reporting under §8(e). The standard in the House version was changed from "causes or contributes to an unreasonable risk" to "causes or significantly contributes to a substantial risk". This particular change was one of several made in TSCA §8 to avoid placing an undue burden on the regulated community. The final changes to focus the scope of Section 8(e) were made in the version reported by the Conference Committee.

The word "substantial" means "considerable in importance, value, degree, amount or extent". Therefore, as generally understood, a "substantial risk" is one which will affect a considerable number of people or portion of the environment, will cause serious injury and is based on reasonably sound scientific analysis or data. Support for the interpretation can be found in a similar provision in the Consumer Product Safety Act. Section 15 of the CPSA defines a "substantial product hazard" to be:

> "a product defect which because of the pattern of defect, the number of defective products distributed in commerce, the severity of the risk, or otherwise, creates a substantial risk of injury to the public."

Similarly, EPA has interpreted the word 'substantial' as a quantitative measurement. Thus, a 'substantial risk' is a risk that can be quantified, *See,* 56 Fed Reg 32292, 32297 (7/15/91). Finally, since information pertinent to the exposure of humans or the environment to chemical substances or mixtures may be obtained by EPA through Sections 8(a) and 8(d) regardless of the degree of potential risk, §8(e) has specialized function. Consequently, information subject to §8(e) reporting should be of a type which would lead a reasonable man to conclude that some type action was required immediately to prevent injury to health or the environment.

Attachment

Comparison:

Reporting triggers found in the 1978 "Statement of Interpretation/ Enforcement Policy",43 Fed Reg 11110 (3/16/78) and the June 1991 *Section 8(e) Guide.*

TEST TYPE	1978 POLICY CRITERIA EXIST?	New 1991 GUIDE CRITERIA EXIST?
ACUTE LETHALITY		
Oral	N}	Y}
Dermal	N}	Y}
Inhalation (Vapors)	}[6]	}[7]
aerosol	N}	Y}
dusts/ particles	N}	Y}
SKIN IRRITATION	N	Y[8]
SKIN SENSITIZATION (ANIMALS)	N	Y[9]
EYE IRRITATION	N	Y[10]
SUBCHRONIC (ORAL/DERMAL/INHALATION)	N	Y[11]
REPRODUCTION STUDY	N	Y[12]
DEVELOPMENTAL TOX	Y[13]	Y[14]

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[6]43 Fed Reg at 11114, comment 14:

"This policy statements directs the reporitng of specifiec effects when unknown to the Administrator. Many routine tests are based on a knowledge of toxicity associated with a chemicalL unknown effects occurring during such a range test may have to be reported if they are those of concern tot he Agency and if the information meets the criteria set forth in Parts V and VII."

[7]Guide at pp.22, 29-31.

[8]Guide at pp-34-36.

[9]Guide at pp-34-36.

[10]Guide at pp-34-36.

[11]Guide at pp-22; 36-37.

[12]Guide at pp-22

[13]43 Fed Reg at 11112

"Birth Defects" listed.

[14]Guide at pp-22

NEUROTOXICITY	N	Y[15]
CARCINOGENICITY	Y[16]	Y[17]
MUTAGENICITY		
In Vitro	Y}[18]	Y} [19]
In Vivo	Y}	Y}
ENVIRONMENTAL		
Bioaccumulation	Y}	N
Bioconcentration	Y}[20]	N
Oct/water Part. Coeff.	Y}	N
Acute Fish	N	N
Acute Daphnia	N	N
Subchronic Fish	N	N
Subchronic Daphnia	N	N
Chronic Fish	N	N
AVIAN		
Acute	N	N
Reproductive	N	N
Reprodcutive	N	N

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[15] Guide at pp-23; 33-34.

[16] 43 Fed Reg at 11112
"Cancer" listed

[17] Guide at pp-21.

[18] 43 Fed Reg at 11112; 11115 at Comment 15
"Mutagenicity" listed/ *in vivo* vs *invitro* discussed; discussion of "Ames test".

[19] Guide at pp-23.

[20] 43 Fed Reg at 11112; 11115 at Comment 16.

CAS # Not known
Chem: oximinoacetone (isonitrosoacetone)
Title: Preliminary toxicity tests on oximinoacetone
Date: 7/23/56
Summary of Effects: convulsions, skin sensitizer

PRELIMINARY TOXICITY TESTS ON OXIMINOACETONE

Medical Research Project No. MR-170

At the request of the Explosives Department, oximinoacetone (isonitrosoacetone) was studied for acute and subacute oral toxicity and acute inhalation toxicity using rats, and for skin irritation and sensitization potential using guinea pigs. The sample tested was given the Haskell number H-1122.

Acute Oral Toxicity

The Approximate Lethal Dose (ALD) for oximinoacetone was found to be 60 mg/kg of body weight for male albino rats when the material was administered by stomach tube as a 0.5 to 10 per cent aqueous solution. Lethal doses caused immediate discomfort, labored respiration, intermittent clonic convulsions, and death within 1 to 24 hours after treatment. The highest doses tested (2250 and 670 mg/kg) caused pulmonary edema and acute gastritis of the type in which the superficial layer of the glandular mucosa was detached or desquamated. Other lethal doses produced no observed anatomical changes. Two of the six animals that received sublethal doses showed evidence of healed gastritis (there was scar tissue in the submucosa) when they were sacrificed ten days after treatment. The others showed no pathological changes.

Subacute Oral Toxicity

Doses of 12 mg/kg of body weight (1/5 ALD) were administered by stomach tube as a 0.25 per cent aqueous solution to each of six male albino rats five times a week for two weeks. Except for a slight initial weight loss, the rats showed no clinical signs. No pathological changes were found when they were sacrificed after the final treatment or ten days later.

Acute Inhalation Toxicity

Adult male albino rats were exposed in a 10-liter bell jar to the mist resulting from vaporization of an aqueous solution (10-20 per cent) of oximinoacetone by means of a DeVilBiss nebulizer. Two rats were used per exposure.

Two rats were exposed to a nominal concentration of 3.6 mg/lit of oximinoacetone (about 1 per cent by volume or 10,000 ppm) at a flow rate of 5 lit/min for a period of 1 hour and 40 minutes. They suffered from dyspnea after one hour of exposure, were comatose within 90 minutes and were dead within two to three hours. There were intermittent convulsions during the exposure and until death. Pathological examinations showed that both rats had brain congestion; in one case there were fresh hemorrhages in the region of the basal ganglia.

Two other rats were exposed for five hours a day on two successive days to concentrations of 1.0 and 1.4 mg/lit (roughly 0.25 and 0.4 per cent by volume) with a flow rate of 4.5 to 5.0 lit/min. One animal had clonic convulsions and became cyanotic after the second treatment. When sacrificed an hour later this animal showed engorgement of blood vessels in the brain and hemorrhage in the subarachnoid spaces, as well as slight distention of the convoluted tubules of the kidney and congestion of the stomach mucosa beneath the squamous epithelium.

A third pair of rats survived a six-hour exposure to a concentration of 1.8 mg/lit (about 0.5 per cent by volume or 5000 ppm) with a flow rate of 3.5 lit/min. No clinical signs were observed and no pathological changes were found when they were sacrificed ten days later.

Skin Irritation and Sensitization

Application of one drop of a 10 per cent aqueous solution of oximinoacetone to the intact shaved skin of guinea pigs produced mild erythema in three, and no irritation in seven of ten guinea pigs. A 25 per cent aqueous solution produced mild erythema in one, and no irritation in nine of ten guinea pigs. A 75 per cent aqueous solution produced no irritation. This phenomenon of greater irritancy from the more dilute aqueous solutions suggests that products of hydrolytic decomposition may be the actual irritants. With abraded skin the reactions were more pronounced, as a 50 per cent aqueous solution produced mild erythema in five of five test animals.

Ten guinea pigs were put through eight sensitizing treatments over a period of two and one-half weeks. With five of the animals the treatment consisted of applications of single drops of a 50 per cent aqueous solution to scratched skin. The remaining five guinea pigs were given intradermal injections of 0.1 ml of a solution in physiological saline; the concentration of test chemical was varied from 0.1 per cent to 3.0 per cent as the treatments proceeded. After a two-week rest period, each animal was challenged by (a) application of a single drop of a 75 per cent aqueous solution to intact shaved skin, (b) intradermal injection of 0.1 ml of a 1 per cent solution in physiological saline, and (c) application of a single drop of 50 per cent aqueous solution to scratched skin.

Evidence for sensitization was not clear cut in the first challenge tests. However, repetition eight days later brought forth much stronger responses. A third challenge test 13 days after the first challenge gave additional strong evidence that the guinea pigs had acquired an allergic sensitization.

Comparison with Hydroxylamine

Since it is known that oximinoacetone decomposes in the presence of water to give pyruvic aldehyde and hydroxylamine, it is of interest to compare the toxicity of the oximinoacetone with that of hydroxylamine, which has been studied as the sulfate salt in earlier work at Haskell Laboratory (MR-225).

The oral ALD of hydroxylamine sulfate for male albino rats was found to be 1000 mg/kg. Clinical signs included cyanosis, labored breathing and poor coordination. With male rabbits the oral ALD was found to be 130 mg/kg; the animals receiving the highest doses showed cyanosis, rapid respiration and, in one case, violent convulsions. With both species in the oral tests, the presence of "brown blood" at autopsy indicated degradation of hemoglobin. This is consistant with literature reports that hydroxylamine induces methemoglobin formation. By skin absorption using male rabbits the ALD was found to be 1500 mg/kg, with clinical signs similar to those of the oral test. At the higher dosages, "brown blood" was noted at autopsy. In the subacute oral test, six of six rats survived ten treatments of 200 mg/kg per day over a two-week period, but showed pallor and cyanosis; on autopsy the animals showed enlargement, darkening and congestion of the spleen. Guinea pig tests for skin reaction showed no primary irritancy with 25 or 50 per cent aqueous solutions, but mild sensitizing properties were revealed.

A comparison of these results for hydroxylamine sulfate with those obtained with oximinoacetone shows some similarity in clinical signs, particularly those dealing with the central nervous system. However, the degradation of hemoglobin noted with hydroxylamine sulfate as evidenced by the presence of "brown blood" at autopsy was entirely missing from the picture in the case of oximinoacetone. Quantitatively, oximinoacetone is of a higher order of toxicity. One may speculate, therefore, that the principal toxic action of oximinoacetone is independent of the possible hydrolysis to give hydroxylamine, and that a specific enzyme-blocking action may be involved.

Summary and Conclusions

The ALD of oximinoacetone was found to be 60 mg/kg when an aqueous solution was administered orally to rats. Lethal doses produced marked discomfort, labored respiration, clonic convulsions, and death in 1 to 24 hours. Very high doses produced acute gastritis and pulmonary edema. Other lethal doses produced no anatomical changes, but the clinical signs suggested effects on the central nervous system. Sublethal doses produced no marked clinical signs. Two of the six animals receiving sublethal doses showed evidence of a healed gastritis; the others showed no pathology.

Doses of 12 mg/kg administered orally to rats five times a week for two weeks produced no clinical signs and no pathological changes.

Acute inhalation toxicity tests revealed that exposure to a nominal concentration of 3.6 mg of oximinoacetone per liter of air, administered at a rate of 5 lit/min for 100 minutes, was lethal to two of two rats studied. They became unconscious and cyanotic, had intermittent clonic convulsions, and died two to three hours after the exposure. No anatomical cause of death was established, but damage had occurred to the brains. The clinical signs were similar to those of the rats receiving oral treatment, indicated an effect on the central nervous system.

Of the two rats which received 1.0 and 1.4 mg/lit at a rate of 4.5 to 5 lit/min for five hours on two successive days, one became cyanotic and convulsive and was sacrificed; anatomical changes were found in the brain, stomach and kidney. The other animal showed no effects. Two other rats survived a six-hour exposure to 1.8 mg/lit at a rate of 3.5 lit/min without harmful effects.

Oximinoacetone is not a strong primary irritant on either intact or abraded skin, but dilute aqueous solutions are more irritating than more highly concentrated solutions. The compound is considered to be a skin sensitizer on the basis of tests on guinea pigs.

From these data, it is evident that oximinoacetone is moderately to highly toxic when administered orally and by inhalation. It is also a potential skin sensitizer. For these reasons, due care must be used in handling this compound. Adequate ventilation must be provided and contact with skin should be avoided. In case the material is spilled on the skin, it should be washed off at once with soap and water.

HASKELL LABORATORY FOR TOXICOLOGY
AND INDUSTRIAL MEDICINE

Report by: JONATHAN W. WILLIAMS
Jonathan W. Williams
Assistant Director

Approved by: John A. Zapp, Jr.
John A. Zapp, Jr.
Director

JWW:ecd
Report No. 28-56
7/23/56

PRELIMINARY TOXICITY TESTS ON OXIMINOACETONE

Medical Research Project No. MR-170

Approved for Pathology:

Douglas M. Gay, M.D.
Chief, Pathology Section

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

Mark H. Christman
Counsel
E. I. Du Pont De Nemours and Company
Legal D-7010-1
1007 Market Street
Wilmington, Delaware 19898

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

APR 18 1995

EPA acknowledges the receipt of information submitted by your organization under Section 8(e) of the Toxic Substances Control Act (TSCA). For your reference, copies of the first page(s) of your submission(s) are enclosed and display the TSCA §8(e) Document Control Number (e.g., 8EHQ-00-0000) assigned by EPA to your submission(s). Please cite the assigned 8(e) number when submitting follow-up or supplemental information and refer to the reverse side of this page for "EPA Information Requests".

All TSCA 8(e) submissions are placed in the public files unless confidentiality is claimed according to the procedures outlined in Part X of EPA's TSCA §8(e) policy statement (43 FR 11110, March 16, 1978). Confidential submissions received pursuant to the TSCA §8(e) Compliance Audit Program (CAP) should already contain information supporting confidentiality claims. This information is required and should be submitted if not done so previously. To substantiate claims, submit responses to the questions in the enclosure "Support Information for Confidentiality Claims". This same enclosure is used to support confidentiality claims for non-CAP submissions.

Please address any further correspondence with the Agency related to this TSCA 8(e) submission to:

Document Processing Center (7407)
Attn: TSCA Section 8(e) Coordinator
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
Washington, D.C. 20460-0001

EPA looks forward to continued cooperation with your organization in its ongoing efforts to evaluate and manage potential risks posed by chemicals to health and the environment.

Sincerely,

Terry R. O'Bryan

Terry R. O'Bryan
Risk Analysis Branch

Enclosure 12036A

Triage of 8(e) Submissions

Date sent to triage: APR 20 1995 NON-CAP (CAP)

Submission number: 12036A TSCA Inventory: Y N (D)

Study type (circle appropriate):

Group 1 - Dick Clements (1 copy total)

ECO AQUATO

Group 2 - Ernie Falke (1 copy total)

(ATOX) (SBTOX) (SEN) (w/NEUR)

Group 3 - Elizabeth Margosches (1 copy each)

STOX CTOX EPI RTOX GTOX

STOX/ONCO CTOX/ONCO IMMUNO CYTO NEUR

Other (FATE, EXPO, MET, etc.): _____

Notes:

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Notes:

Contractor reviewer : PRR **Date:** 4/3/95

CECATS\TRIAGE TRACKING DBASE ENTRY FORM

CECATS DATA:
Submission # 8EHQ- 1092 - 12036 SEQ. A

TYPE: INT. SUPP FLWP

SUBMITTER NAME: E. I. Dupont de Nemours and Company

INFORMATION REQUESTED: FLWP DATE:
0501 NO INFO REQUESTED
0502 INFO REQUESTED (TECH)
0503 INFO REQUESTED (VOL ACTIONS)
0504 INFO REQUESTED (REPORTING RATIONALE)

DISPOSITION:
0638 REFER TO CHEMICAL SCREENING
0678 CAP NOTICE

VOLUNTARY ACTIONS:
0401 NO ACTION REPORTED
0402 STUDIES PLANNED/UNDERWAY
0403 NOTIFICATION OF WORKERS/OTHERS
0404 LABEL/MSDS CHANGES
0405 PROCESS/HANDLING CHANGES
0406 APP./USE DISCONTINUED
0407 PRODUCTION DISCONTINUED
0408 CONFIDENTIAL

SUB. DATE: 10/15/92 OTS DATE: 10/27/92 CSRAD DATE: 03/06/95

CHEMICAL NAME:
Acetone, oximino —
Acetone, isonitroso —

CAS#
~~[illegible]~~ 306-44-5 per CASontine
11

INFORMATION TYPE:		P F C
0201	ONCO (HUMAN)	01 02 04
0202	ONCO (ANIMAL)	01 02 04
0203	CELL TRANS (IN VITRO)	01 02 04
0204	MUTA (IN VITRO)	01 02 04
0205	MUTA (IN VIVO)	01 02 04
0206	REPRO/TERATO (HUMAN)	01 02 04
0207	REPRO/TERATO (ANIMAL)	01 02 04
0208	NEURO (HUMAN)	01 02 04
0209	NEURO (ANIMAL)	01 02 04
0210	ACUTE TOX. (HUMAN)	01 02 04
0211	CHR. TOX. (HUMAN)	01 02 04
0212	ACUTE TOX. (ANIMAL)	01 02 04
0213	SUB ACUTE TOX (ANIMAL)	01 02 04
0214	SUB CHRONIC TOX (ANIMAL)	01 02 04
0215	CHRONIC TOX (ANIMAL)	01 02 04

INFORMATION TYPE:		P F C
0216	EPI/CLIN	01 02 04
0217	HUMAN EXPOS (PROD CONTAM)	01 02 04
0218	HUMAN EXPOS (ACCIDENTAL)	01 02 04
0219	HUMAN EXPOS (MONITORING)	01 02 04
0220	ECO/AQUA TOX	01 02 04
0221	ENV. OCCC/REL/FATE	01 02 04
0222	EMER INCI OF ENV CONTAM	01 02 04
0223	RESPONSE REQEST DELAY	01 02 04
0224	PROD/COMP/CHEM ID	01 02 04
0225	REPORTING RATIONALE	01 02 04
0226	CONFIDENTIAL	01 02 04
0227	ALLERG (HUMAN)	01 02 04
0228	ALLERG (ANIMAL)	01 02 04
0239	METAB/PHARMACO (ANIMAL)	01 02 04
0240	METAB/PHARMACO (HUMAN)	01 02 04

INFORMATION TYPE:		P F C
0241	IMMUNO (ANIMAL)	01 02 04
0242	IMMUNO (HUMAN)	01 02 04
0243	CHEM/PHYS PROP	01 02 04
0244	CLASTO (IN VITRO)	01 02 04
0245	CLASTO (ANIMAL)	01 02 04
0246	CLASTO (HUMAN)	01 02 04
0247	DNA DAM/REPAIR	01 02 04
0248	PROD/USE/PROC	01 02 04
0251	MSDS	01 02 04
0299	OTHER	01 02 04

TRIAGE DATA:

NON-CBI INVENTORY
YES
CAS SR
NO
IN TERMINI
COMPLETE

ONGOING REVIEW
YES (DROP/REFER)
NO (CONTINUE)
REFER

SPECIES
RAT
GP

TOXICOLOGICAL CONCERN:
LOW
MED
HIGH

USE:

PRODUCTION:

8(E)-12036A

M/L/L/M/L/L/M

ACUTE ORAL TOXICITY IN MALE ALBINO RATS IS OF MEDIUM CONCERN BASED ON LETHALITY AT DOSES AS LOW AS 60 MG/KG. DOSAGES (GAVAGE) AS HIGH AS 670 MG/KG AND 2250 MG/KG, PRODUCED PULMONARY EDEMA AND ACUTE GASTRITIS. SUBLETHAL DOSES SHOWED EVIDENCE OF HEALED GASTRITIS AT NECROPSY. MORTALITY INCIDENCE, GROUP SIZE, AND SPECIFIC DOSAGES WERE NOT REPORTED.

SUBACUTE ORAL TOXICITY IN MALE ALBINO RATS IS OF LOW CONCERN. DOSAGE (GAVAGE, 5/WEEK FOR 2 WEEKS) AND MORTALITY DATA WERE 12 MG/KG (0/6). EXCEPT FOR A SLIGHT INITIAL WEIGHT LOSS, NO CLINICAL SIGNS OR PATHOLOGICAL CHANGES WERE OBSERVED.

ACUTE INHALATION TOXICITY IN MALE RATS IS OF LOW CONCERN BASED ON MORTALITY. DOSAGE (1-HOUR AND 40 MINUTES) AND MORTALITY WERE 3.6 MG/L (2/2). DOSAGE (6-HOURS) AND MORTALITY WERE 1.8 MG/L (0/2). TOXIC SIGNS INCLUDED DYSPNEA, CONVULSIONS, AND COMA. PATHOLOGY REVEALED BRAIN CONGESTION AND HEMORRHAGES IN THE REGION OF THE BASAL GANGLIA (ONE RAT).

SUBACUTE INHALATION TOXICITY IN RATS (SEX NOT REPORTED) IS OF MEDIUM CONCERN BASED ON PATHOLOGICAL RESPONSES. 2 RATS WERE EXPOSED FOR FIVE HOURS A DAY ON TWO SUCCESSIVE DAYS TO CONCENTRATIONS OF 1.0 AND 1.4 MG/L. ONE ANIMAL HAD CLONIC CONVULSIONS AND BECAME CYANOTIC AFTER THE SECOND TREATMENT. WHEN SACRIFICED AN HOUR LATER THIS ANIMAL SHOWED ENGORGEMENT OF THE BLOOD VESSELS IN THE BRAIN AND HEMORRHAGE IN THE SUBARACHNOID SPACES, AS WELL AS SLIGHT DISTENTION OF THE CONVOLUTED TUBULES OF THE KIDNEY AND CONGESTION OF THE STOMACH MUCOSA BENEATH THE SQUAMOUS EPITHELIUM. EFFECTS ON THE SECOND RAT WERE NOT REPORTED.

ACUTE INHALATION TOXICITY IN RATS (SEX NOT REPORTED) IS OF LOW CONCERN. TWO RATS WERE EXPOSED FOR 6 HOURS TO A CONCENTRATION OF 1.8 MG/L. NO CLINICAL SIGNS WERE OBSERVED AND NO PATHOLOGICAL CHANGES WERE FOUND WHEN SACRIFICED 10 DAYS LATER.

SKIN IRRITATION IN GUINEA PIGS IS OF LOW CONCERN BASED ON MILD ERYTHEMA (1/10) AND NO IRRITATION (9/10) FROM EXPOSURE TO ONE DROP OF 25% SOLUTION; NO IRRITATION (INCIDENCE NOT GIVEN) FROM EXPOSURE TO ONE DROP OF 75% SOLUTION; AND MILD ERYTHEMA (5/5) FROM EXPOSURE TO 50% SOLUTION ON ABRADED SKIN.

SKIN SENSITIZATION IN GUINEA PIGS IS OF MEDIUM CONCERN BASED ON A MODERATE SENSITIZATION RESPONSE AND NO EVIDENCE THAT THE SUBSTANCE IS A SENSITIZER IN HUMANS. A GROUP OF 5 GUINEA PIGS WAS TREATED 8 TIMES OVER 2.5 WEEKS WITH A SINGLE DROP OF A 50% OF TEST SUBSTANCE TO ABRADED SKIN, WHILE A SECOND GROUP OF 5 WAS GIVEN INTRADERMAL INJECTION OF 0.1 ML OF A 0.1 TO 3% SOLUTION. FOLLOWING A TWO WEEK REST PERIOD THE ANIMALS WERE CHALLENGE BY A SINGLE DROP OF A 50 OR 75% SOLUTION TO ABRADED OR INTACT SKIN, RESPECTIVELY, OR AN INTRADERMAL INJECTION OF 0.1 ML OF A 1% SOLUTION. EQUIVOCAL

EVIDENCE OF SENSITIZATION WAS OBSERVED DURING THIS CHALLENGE, WITH STRONGER EVIDENCE OF SENSITIZATION OBSERVED FOLLOWING CHALLENGES 8 AND 13 DAYS AFTER THE INITIAL CHALLENGE. RESPONSE INCIDENCES WERE NOT GIVEN.